sometimes difficult decision about long term anticoagulation more rational.

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Prostate Carcinoma: Clarification Through Clinical Insight and Molecular Diagnostics

THE DILEMMAS SURROUNDING CARCINOMA of the prostate (CaP) screening and treatment are a source of professional debate and confusion, and fear for patients and their wives. Four recent developments provide guideposts to reduce uncertainty.

First, the epidemic is waning. Predictions by the American Cancer Society of 334,500 cases in 1997 were high; actually fewer than 210,000 cases were diagnosed. The incidence is lower because the earlier diagnosis of preclinical or latent cancers by serum PSA screening has been completed and these patients are thus removed from each year's new count. No prediction is possible of the ultimate level of decline. However the increase of CaP in men over the age of 70 (years) and our belief that there are environmental factors increasing the incidence of CaP suggests that we will not return to pre PSA testing levels of the disease.

Second, we know that patient characteristics are important in deciding whether to use PSA to screen for CaP. If men are to benefit from CaP screening and treatment, they must have a reasonable likelihood of surviving more than 10–15 years. Thus perhaps as important as age exclusion may be the exclusion from PSA testing of men with poor health and/or prospects e.g. heavy cigarette smokers. In addition a brief written informed consent prior to PSA testing describing the consequences of CaP diagnosis may reduce patient interest in the procedure. However, a substantial proportion might choose to proceed with testing, presumably with an improved attitude regarding intervention if and when CaP is found.

Third, modifications of PSA testing designed to improve the predictive value of the test continue to be reported. PSA density, age specific values, and PSA velocity have not been confirmed to enhance specificity and sensitivity. PSA circulates bound to serum proteins. A reduced ratio of free to bound PSA improves the distinction between malignant and benign causes of PSA elevation. CaP can be detected even in men with PSA levels less than 4.0 ng/mL.

Fourth, research may help to distinguish apples from oranges. Although the Gleason score on pathology examination remains the most important predictor of metastatic potential in cohorts of patients, individual variation is sufficient to reduce assuredness that local-regional therapy alone will be curative. Nomograms that combine Gleason score, serum PSA and clinical stage have been reported to refine the prediction of organ confined disease. As with other aspects of oncology, these nomograms are readily available to patients on the Internet but they have not been validated to improve survival.

There is now a catalog of molecular alterations that are beginning to distinguish familial from sporadic and indolent from progressive cancer, as well as local regional neoplasia from disseminated and androgen sensitive from androgen insensitive cancer. The locus for a major prostate cancer susceptibility gene resides on chromosome 1. Mutation in the tumor suppressor gene p53 can be identified in 40% of primary CaP and greater than 70–80% of metastatic CaP cells. Patients at relapse are not human-androgen receptor (hAR) negative but overexpress the hAR protein, a phenomenon that reflects gene amplification.

Alterations in gene expression begin to provide a cohesive explanation for the remarkable variation in the biology of CaP. Patient education will now have to extend from informed consent around PSA testing to the nuances of tumor suppressor genes and hormone receptors.

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Finding the Iron in the Melting Pot—Practical Use of a New Genetic Assay for Hereditary Hemochromatosis

HEMOCHROMATOSIS IS A SYNDROME characterized by excessive iron accumulation. Left untreated, it is associated with progressive dysfunction of multiple organs including the heart, pituitary, pancreas and liver. Resultant diabetes and cirrhosis account for most of the associated mortality. A genetic basis for many cases of hemochromatosis has long been recognized. Linkage to